Therapeutic Strategies for Localized and Locally Advanced Prostate Cancer: Combining Androgen Suppression with Definitive Local Therapy

Anthony V. D'Amico, MD, PhD

Brigham and Women's Hospital and Dana Farber Cancer Institute, Boston, MA

Additional Contributors

Howard M. Sandler, MD, Richard G. Stock, MD, Nelson Stone, MD

Patients with locally advanced prostate cancer (clinical category T3,4) managed with external beam radiation therapy (EBRT) and 3 years of androgen suppression therapy (AST) compared with patients managed with EBRT alone have been shown to have a survival benefit. Studies addressing the same question in patients with clinically localized disease (T1,2) are now completed and await follow-up. A decrease in positive surgical margins has been noted; however, no benefit in prostate-specific antigen (PSA) control has been documented in any of several randomized studies in which the addition of 3 months of neoadjuvant AST was administered before radical prostatectomy. Randomized data now show that dose-escalated radiation provides superior PSA control rates compared with conventional-dose radiation therapy for patients with localized prostate cancer. How best to administer high-dose radiation (eg, intensity modulated radiation therapy, or 3-dimensional conformal radiation therapy with or without a brachytherapy boost), and how best to integrate high-dose radiation for patients with high-risk localized or locally advanced prostate cancer remain under investigation.

[Rev Urol. *5(suppl 6):S40-S46*]

© 2003 MedReviews, LLC

Key words: Prostate cancer • External beam radiation therapy • Androgen suppression therapy • Prostate-specific antigen

The rationale for combining external beam radiation therapy (EBRT) and androgen suppression therapy (AST) for the treatment of prostate cancer is 2-fold. First, elimination of androgen-dependent clones within the primary tumor increases the probability that a given dose of EBRT will sterilize the entire

Table 1
Synopsis of Completed Phase 3 Trials Examining the Efficacy of Combined Androgen Deprivation Therapy and External Beam Radiation Therapy in the Management of Locally Advanced Prostate Cancer

			P-Value				
Title	Rx Arms	Patient Selection Criteria	5-Year Local Control	5-Year Distant Control	5-Year PSA Control	5-Year Cancer-Specific Survival	5-Year Overall Survival
RTOG 8531	Goserelin (lifetime vs none)	Clinical stage T3, path stage T3 (15%), node positive (28%)	<.0001	<.0001	<.0001	.23 (overall) .019* bGleason 8–10* (central review)	.36 (overall) .036* bGleason 8–10* (central review)
RTOG 8610	Goserelin (4 mo vs none)	Clinical stage ≥ Tb and >25 cm^2 tumor	.016	.04	<.001	.05 (overall) .0002* bGleason ≤6 (central review)*	.10 (overall) .015* bGleason ≤6 (central review)*
EORTC 22863	Goserelin (3 years vs none)	Clinical stage T1,2 and high grade (9%), clinical stage T3,4 and low–intermediate grade (91%)	<.001	<.001	<.001	<.001	<.001
RTOG 9202*	Goserelin (2 years vs none)	Clinical stage T2 and >25 cm^2 tumor, clinical stage T3,4	.0001	.001	.0001	.07 (overall) .007 bGleason ≥8	ns (overall) .02 bGleason ≥8
RTOG 9413	Goserelin or lupron plus flutamide (4 mo)‡	Clinical stage T1b-4	na	na	.0005‡	na	0.15

Rx, treatment; na, not available; bGleason, biopsy Gleason score.
*All patients received 4 months of goserelin and flutamide before randomization.
‡Two months before and 2 months during external beam radiation therapy (EBRT) or 4 months after EBRT. Patients eligible for RTOG 9413 must not be eligible for RTOG 9408 and therefore if the patient has clinical stage T1b-2b they must also have a PSA >20 ng/mL.
‡This advantage was seen in the neoadjuvant and pelvic radiotherapy arm.

local tumor burden. Second, occult micrometastatic disease unaddressed by the local therapy (radiation) might be eradicated through the use of the systemic therapy (androgen suppression).

Locally Advanced Prostate Cancer

Over the last several years, a number of reports documenting the benefit in overall survival from the use of combined EBRT and AST for patients with locally advanced prostate cancer have been published. Table 1 is a compilation of completed EBRT studies evaluating the role of neoadjuvant and/or adjuvant AST in the treatment of locally advanced prostate cancer.

Randomized Trials of Combination EBRT and AST

The Radiation Therapy Oncology Group (RTOG) trial 8531[1] enrolled 977 patients (945 evaluable) with clinical stage T3 disease (57%), postprostatectomy patients with seminal vesicle or extracapsular disease with margin involvement (15%), and patients with stage D1 (node positive) disease (28%). The randomization was to either indefinite AST with goserelin or no AST, after the administration of external radiation therapy. Results show a statistically significant improvement in local (P <.0001), biochemical (P <.0001), and distant (P <.0001) control at 5 years. A numeric but not statistically significant (P = 0.52) improvement in overall survival was noted for all patients.

In a subgroup of patients with a centrally reviewed biopsy Gleason score of 8 to 10, there was a signifi-

cant difference in overall survival (P = .03). However, this result was not conclusive. Patients were randomized on the basis of institutional rather than central pathology review, and 27% of patients with institutional pathology review with biopsy Gleason scores of 8 to 10, when centrally reviewed, had scores of 7 or less.[2] When the study was analyzed based on the institutional pathology review (on which the randomization was based), the survival benefit noted for patients with a central pathology biopsy Gleason score of 8 to 10 was lost.

RTOG 8610[3] enrolled 471 patients (456 evaluable) with clinical stage T2b or higher who had at least 25 cm^2 of palpable disease. The randomization was to external beam radiation therapy with or without 4 months of goserelin and the antiandrogen flutamide (2 months before and 2 months during radiation therapy). At a median follow-up of 6.7 years, a statistically significant increase has been noted in local (P = .016), biochemical (P <.0001) and distant control (P = .04). A cause-specific survival had also been noted at 5 years (90% vs 85%, P = .05). Subset analysis indicated that there was a benefit in overall survival at 5 years for patients whose biopsy Gleason score was less than or equal to 6 (70% vs 52%, P = .015) treated with EBRT and AST as compared with EBRT only. A numeric (72% vs 68%) but not statistically significant (P = .10) improvement in overall survival was noted at 5 years.

It is important to note that the use of short-term hormonal therapy (4 months) did not lessen the response to salvage hormonal therapy (if needed) subsequently. Specifically, Shipley and colleagues[4] reported that the overall 5-year and 3-year disease-free survival after salvage hormonal therapy for patients in either arm of RTOG 8610 were not significantly different (overall: 39% vs 40%; disease free: 21% vs 23%).

The European Organization for Research on Treatment of Cancer (EORTC 22863)[5] recently reported an improvement in the estimated overall 5-year survival for patients receiving 3 years of adjuvant subtotal androgen suppression (goserelin) and 1 month of cyproterone acetate as compared with those receiving no adjuvant treatment after large-field EBRT (79% vs 62%, P = .001). The trial enrolled patients in clinical stage T1 and T2 with poorly differentiated tumors (9%), and clinical stage T3 and T4 patients with well- or moderately-well-differentiated tumors (91%). Of 415 patients, 401 were evaluable, and the median follow-up was 45 months. At 5 years, there were statistically significant improvements in local control (97% vs 77%, P <.001) and metastasis-free survival (85% vs 48%, P <.001) among patients who received AST. However, data on the timing of salvage androgen suppression in the EBRT group is uncertain. Whether salvage hormonal therapy was given at the time of PSA failure, positive bone scan, biopsy proven local recurrence, or at the time of clinical symptomatic progression was not stated in the report.

Subset analysis of RTOG 8610 indicated that there was a benefit in overall survival at 5 years for patients whose biopsy Gleason score was less than or equal to 6 (70% vs 52%, P = .015) treated with EBRT and AST as compared with EBRT only.

RTOG 9202,[6] completed in 2000, studied patients with clinical stage T2b–T4 disease. All patients received 4 months of total AST (goserelin and flutamide) before (2 months) and during EBRT (2 months). Patients were then randomized to an additional 2 years of continued goserelin after EBRT versus none. At a median follow-up of 4.8 years, there were statistically significant differences in local (P = .0001), distant (P = .001), and PSA control (P = .0001). Disease-specific and overall survival differences were not reported for the entire study population, but rather only for the subgroup with Gleason scores of 8 or more (disease-specific survival: 90% vs 78%, P = .007; overall survival: 80% vs 69%, P = .02).

Therefore, for patients with biopsy Gleason score of 6 or less, 4 months of AST is adequate for a survival benefit in approximately 5% of patients, and longer durations are needed to see a survival benefit in men with higher biopsy Gleason scores, as per RTOG 9202. Whether durations longer than 4 months in patients with a biopsy Gleason score of 6 or less are needed, or whether 2 years and 4 months of hormones for patients with biopsy Gleason score of 8 or more is too long remains unanswered.

A similar concern regarding the survival benefit in biopsy Gleason score of 6 or less can be raised in this study, as noted for RTOG 8531. In particular, the survival benefit was noted based on central pathology review and not on the institutional Gleason score on which the randomization was based. The survival benefit might not be present when analyzed based on the institutional Gleason score. To date, this analysis has not been reported, and the results of RTOG 9202, in which the analysis and randomization were both based on the institutional

Gleason score to ascertain whether long-term (4 months and 2 years) versus short-term (4 months) hormonal therapy have a survival benefit in locally advanced patients with Gleason score 7 or less, are awaited.

RTOG 9413[7] was a 4-arm, randomized trial that enrolled 1323 patients with clinical stage T2c–4 disease with a pretreatment PSA of 100 ng/mL or less between 1995 and 1999. To be eligible, patients needed to have more than a 15% risk of lymph nodal involvement using the equation $^2/_3$ PSA + [(Gleason score − 6) × 10]. All patients received 4 months of combined hormonal blockade and conventional-dose EBRT (approximately 70 Gy). The two randomizations were 2 months of neoadjuvant and concurrent versus 2 months concurrent and 4 months of adjuvant hormonal therapy, and a prostate field versus an initial pelvic examination followed by prostate EBRT. The results at 5 years showed that the pelvic EBRT field and neoadjuvant hormonal therapy arm had a significant advantage in terms of progression-free survival (PFS) (61% vs 45%–49%, P = .0005). However, no advantage in any treatment arm has been noted to date for overall survival (88% vs 81%–83%, P = .15). Given the advantage in PFS based on PSA progression, this question arises: In whom is this PFS benefit likely to translate into a benefit in cancer-specific survival (CSS) and overall survival? The likely population in whom a PFS benefit might translate into a CSS and overall survival benefit would be those men with advanced disease and at least a 10-year life expectancy.

The data from this trial included patients whose median age was 70 and whose median PSA was 22.8 ng/mL. In addition, 67% of the patients had T2c–T4 disease, and 72% had at least a biopsy Gleason score of 7. In other words, patients were elderly with advanced disease. As a result, further follow-up will be necessary to determine whether the PFS benefit will translate into a benefit in CSS and overall survival. In conclusion, based on the findings from this study, pelvic radiotherapy and neoadjuvant and concurrent AST should be discussed and offered to patients with at least a 10-year life expectancy and clinically localized but high-risk disease.

Randomized trials of short-term hormonal therapy in addition to external beam radiation for patients with clinically localized disease await further follow-up.

Retrospective Cohort Studies of EBRT and Brachytherapy with AST

Although the results of prostatectomy, EBRT, and brachytherapy are excellent in low-risk patients (PSA <10 ng/mL, Gleason score 6 or less and stage T2a or less), these modalities do not yield as favorable a result in locally advanced disease. In a retrospective review of more than 1800 localized prostate cancer cases, D'Amico and colleagues[8] found substantially inferior outcomes for all three treatments when high-risk prostate cancer patients were treated.

The search for improved treatment strategies for these patients with high-risk localized or locally advanced disease has included multiple approaches. First, short-term hormonal therapy (3 months) in combination with radical prostatectomy, which at first seemed attractive because of the significant reduction in margin positivity rates,[9] proved disappointing when PSA failure was not improved.[10] Longer hormonal therapy usage might improve these results; however, data are not yet available. Likewise, randomized trials of short-term hormonal therapy in addition to EBRT for patients with clinically localized disease await further follow-up. However, long-term hormonal therapy has been shown to be successful when combined with EBRT in patients with locally advanced disease.[5] In addition, higher EBRT doses (75–76 Gy) have been shown to prolong PSA control[11] and decrease the posttreatment prostate positive biopsy rate.[12]

Laverdiere and coworkers[13] demonstrated a decrease in positive postirradiation (EBRT) prostate biopsies with increasing time of exposure to androgen deprivation therapy (ADT). Stone and Stock[14] demonstrated a reduction in the 2-year postimplant positive biopsy rate from 21.1% to 3.4% (P = .003) with the use of 6 months of ADT combined with either I-125 or Pd-103 brachytherapy. Higher radiation doses have also been shown to have a positive impact on local control. Stock and colleagues[15] demonstrated a dose–response reduction in postimplant positive biopsies in patients treated with I-125 and Pd-103. Thus, the rationale exists to combine both high radiation doses with ADT to improve local control rates.

Cancer control was the subject of a recently reported 85-patient study of high-risk prostate cancer patients (PSA >15 ng/mL, score ≥8, stage T2c–T3, or positive seminal vesicle biopsy) with negative bone scans.[16] Presenting PSA (median 13.7) levels were 0–4 in 3%, >4–10 in 33%, >10–20 in 28%, >20–50 in 25%, and >50 in 11%. Gleason scores were 2–4 in 2%, 5–6 in 28%, 7 in 35%, and 8–10 in 35%. Clinical stages were T1c in 15%, T2a in 12%, T2b in 19%, T2c in 40% and T3 in 14%. Twenty-four patients (28%) had positive seminal

vesicle biopsies. Those patients with a positive seminal vesicle biopsy also had the seminal vesicles implanted with Pd-103 seeds. Follow-up from completion of hormonal therapy to last visit ranged from 2 to 6 years (median 3 years). PSA failure was calculated by the actuarial method of Kaplan and Meier and the American Society for Therapeutic Radiology and Oncology definition.

The 3-year estimate of PSA failure-free survival was 83%. Patients with Gleason scores of 8–10 did significantly worse compared with patients with Gleason scores of 7 or less (70% vs 90%, P = .05). Patients with seminal vesicle invasion and Gleason scores 8 to 10 had the worse prognosis, with a 3-year estimate of freedom from PSA failure of 45%, compared with 85% for the remaining patients (P = .005). Testosterone levels drawn at last follow-up fell within the normal range (>150 ng/dL) in 85% of patients. However, prospectively collected toxicity data are not yet available.

The combined-modality regimen of intermediate hormonal therapy (9 months), permanent seed implant, and conformal external beam irradiation seems promising.[16] Testosterone levels return to normal in most patients, minimizing the side effects of persistent androgen deprivation. The subgroup of high-risk patients with a Gleason score of 8 to 10 in the seminal vesicles might benefit from longer hormonal therapy or the addition of a chemotherapy strategy. A larger, prospective randomized trial will be needed to test this hypothesis and to determine whether the addition of ADT to high-dose radiation therapy (EBRT and brachytherapy) will improve survival in high-risk patients, compared with the current standard of EBRT and ADT, and at what cost to the patient's health-related quality of life.

Localized Prostate Cancer

Questions regarding the long-term efficacy, duration, and timing of ADT when used in conjunction with EBRT in the treatment of clinically localized prostate cancer remain unanswered. However, these questions have been answered in part in the setting of radical prostatectomy.

Questions regarding the long-term efficacy, duration, and timing of androgen deprivation therapy when used in conjunction with EBRT in the treatment of clinically localized prostate cancer remain unanswered.

Randomized Trials of Neoadjuvant AST and Radical Prostatectomy

There have been several published randomized studies[9,10,17] evaluating the ability of 3 months of neoadjuvant AST to impact the pathologic and cancer control outcomes after radical prostatectomy in patients with clinical category T1–T3 disease. The message from these studies has been clear. Specifically, 3 months of neoadjuvant AST decreased the margin positive rate but had no impact on cancer control. In particular, the PSA control rates up to 5 years after radical prostatectomy, with or without 3 months of neoadjuvant AST, have not been significantly different. Whether the decrease in positive surgical margins is real or a result of the difficulty in assessing pathologic margins in the setting of a prostate gland that has been treated with AST remains controversial. Given the lack of a difference in cancer control outcomes, however, the current standard is not to recommend the short-term (3 months) use of neoadjuvant AST in patients planning to undergo radical prostatectomy.

Longer durations of neoadjuvant AST have also been studied. Specifically, a randomized study[18] of 3 versus 8 months of neoadjuvant AST has been completed in patients with clinically localized adenocarcinoma of the prostate. This trial showed a significant reduction in the positive surgical margin rate, from 23% to 12% (P = .01) for patients who received 3 versus 8 months of neoadjuvant AST, but no cancer control outcomes have yet been reported. Further follow-up of this study will address the question of the impact of duration of neoadjuvant AST on cancer control in the surgical setting.

Prospective Randomized Trials of EBRT with or without AST

The prospective randomized trials (RTOG 9408, DFCI 95096), conducted to validate the use of combined EBRT and AST, are now complete and are listed in Table 2. The RTOG study 9408 had exactly the same randomization as RTOG 8610. Specifically, patients were randomized to receive EBRT alone or in conjunction with 2 months of neoadjuvant and 2 months of concurrent goserelin and flutamide. Patient selection criteria were based on both clinical stage (T1b–T2b) and PSA level (<20 ng/mL).

The combined-modality regimen of intermediate hormonal therapy (9 months), permanent seed implant, and conformal external beam irradiation seems promising.

Table 2
Synopsis of Completed Phase III Trials Examining the Efficacy of Combined Androgen Deprivation Therapy Plus EBRT in the Management of Localized Prostate Cancer

Title	Rx Arms	Patient Selection Criteria
RTOG 9408	Goserelin, flutamide (4 months vs none)	Clinical stage T1b–T2b and PSA <20 ng/mL
DFCI 95096	Goserelin, flutamide (6 months vs none)	Clinical stage T1b–T2b and PSA >10* or bGleason ≥7

Results from these trials are not yet available.
*Maximum PSA = 40 ng/mL. Patients are also eligible if endorectal coil MR stage T3 and PSA >4–10 ng/mL and biopsy Gleason score (bGleason) 5 or 6.
EBRT, external beam radiation therapy.

Approximately 2000 people were enrolled, making this the largest study in clinically localized prostate cancer to date.

D'Amico and colleagues[19] have completed a phase III trial (DFCI 95096) of EBRT with or without 6 months of lupron and flutamide (2 months before, during, and after EBRT). All patients at high risk for postoperative PSA failure were eligible if their 2-year freedom from postoperative PSA failure (according to an actuarial calculation) was, at best, only 50% after EBRT alone. Other patient eligibility criteria are shown in Table 2.

Until the results of these prospective, randomized trials are available, it remains unknown whether a survival benefit will occur as a result of the use of AST in conjunction with EBRT alone as opposed to EBRT for patients with clinically localized disease.

Randomized Trials Evaluating the Duration of AST

Two additional studies have been performed to assess the impact that the duration of AST has on cancer control for patients with clinical category T1-2 disease treated with EBRT. Specifically, RTOG 9910 is nearing completion of a trial of 4 versus 8.5 months of AST, and Crook and colleagues[20] in Canada have completed and reported the preliminary findings of a randomized study of 3 versus 8 months of neoadjuvant AST. The main difference between these two studies is that all of the AST was given before EBRT in the Canadian study, whereas in the RTOG study the AST was neoadjuvant and concurrent. Perhaps this provides the explanation for the lack of a difference in 3-year actuarial freedom from failure (65% vs 64%) in the Canadian study. Further follow-up of both of these studies will help to clarify whether the duration and the timing of AST (neoadjuvant vs neoadjuvant and concurrent) can impact survival in the setting of an EBRT-managed patient with clinically localized disease. ■

References

1. Lawton CA, Winter K, Murray K, et al. Updated results of the phase III Radiation Therapy Oncology Group (RTOG) trial 8531 evaluating the potential benefit of androgen suppression therapy following standard radiation therapy for unfavorable prognosis prostate cancer. *Int J Radiat Oncol Biol Phys.* 2001;49:937–946.

Main Points

- The use of androgen suppression therapy (AST) in patients undergoing external beam radiation therapy (EBRT) increases the probability that EBRT will sterilize the entire local tumor burden, as well as eradicate micrometastatic disease that is untreated by localized EBRT.
- EBRT plus 4 months of AST in patients with a biopsy Gleason score of 6 or less produces a survival benefit in approximately 5% of patients. Longer durations of androgen suppression might be required in patients with higher Gleason scores; however, the optimal duration of therapy awaits elucidation.
- Follow-up results from clinical trials are needed to determine the optimal duration of AST in EBRT-managed patients with clinically localized disease (T1,2).
- Among patients with a 10-year or more life expectancy and clinically localized, high-risk disease, pelvic radiotherapy plus concurrent and neoadjuvant androgen suppression might be beneficial.
- EBRT plus 3 years of AST produces a greater survival benefit than EBRT alone in patients with locally advanced prostate cancer (clinical category T3,4).
- There currently is no evidence to support the use of neoadjuvant AST prior to radical prostatectomy in patients with clinically localized disease.

2. Grignon D. Paper presented at: Second International Conference on Neoadjuvant Hormonal Therapy for Prostate Cancer; November 2000; Boston, MA.
3. Pilepich MV, Winter K, John MJ, et al. Phase III Radiation Therapy Oncology Group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys*. 2001;50:1243–1252.
4. Shipley WU, Lu JD, Pilepich MV, et al. Does neoadjuvant hormone treatment compromise subsequent androgen suppression in prostate cancer patients who fail initial radiation therapy: a secondary analysis of RTOG 86-10 [abstract]. *Int J Radiat Oncol Biol Phys*. 2000;48:169.
5. Bolla M, Gonsalez D, Warde P, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med*. 1997;337:295–300.
6. Hanks GE, Lu J, Machtay M, et al. RTOG Protocol 92-02: a phase III trial of the use of long-term androgen suppression following neoadjuvant hormonal cytoreduction and radiotherapy for locally advanced carcinoma of the prostate [abstract]. *J Clin Oncol*. 2000;19:327a.
7. Roach M 3rd, DeSilvio M, Lawton C, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant conbined androgen suppression: Radiation Therapy Oncology Group 9413. *Int J Radiat Oncol Biol Phys*. 2003;21:1904-1911.
8. D'Amico AV, Schultz D, Loffredo M, et al. Biochemical outcome following external beam radiation therapy with or without androgen suppression therapy for men with clinically localized prostate cancer. *JAMA*. 2000;284:1280–1283.
9. Bono AV, Pagano F, Montironi R, et al. Effect of complete androgen blockade on pathologic stage and resection margin status of prostate cancer: progress pathology report of the Italian PROSIT study. *Urology*. 2001;57:117–121.
10. Soloway MS, Pareek K, Sharifi R, Wajsman Z. Neoadjuvant androgen ablation before radical prostatectomy in cT2bNxMo prostate cancer: 5-year results. *J Urol*. 2002;167:112–116.
11. Pollack A, Zagars GK, Smith LG, et al. Preliminary results of a randomized radiotherapy dose-escalation study comparing 70 Gy with 78 Gy for prostate cancer. *J Clin Oncol*. 2000;18: 3504–3911.
12. Zelefsky MJ, Fuks Z, Hunt M, et al. High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. *J Urol*. 2001; 166:876–881.
13. Laverdiere J, Gomez JL, Cusan L, et al. Beneficial effect of combination hormonal therapy administered prior and following external beam radiation therapy in localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 1997;37:247–252.
14. Stone NN, Stock RG. Prostate brachytherapy: treatment strategies. *J Urol*. 1999;162:421–426.
15. Stock RG, Stone NN, Tabert A, et al. A dose-response study for I-125 prostate implants. *Int J Radiat Oncol Biol Phys*. 1998;41:101–108.
16. Stock RG, Stone NN, Hong S. Is long term hormonal therapy needed with dose escalation in high risk prostate cancer? Results of treatment with 9 months of hormonal therapy, brachytherapy and 3D conformal external beam irradiation. *Int J Radiat Oncol Biol Phys*. 2001;51:2127a.
17. Aus G, Abrahamsson PA, Ahlgren G, et al. Three-month neoadjuvant hormonal therapy before radical prostatectomy: a 7-year follow-up of a randomized controlled trial. *Br J Urol*. 2002;90:561–566.
18. Gleave ME, Goldenberg SL, Chin JL, et al. Randomized comparative study of 3 versus 8-month neoadjuvant hormonal therapy before radical prostatectomy: biochemical and pathological effects. *J Urol*. 2001;166:500–506.
19. D'Amico AV. Combined-modality staging for localized adenocarcinoma of the prostate. *Oncology*. 2001;8:1049–1059.
20. Crook JM, Ludgate C, Lim J, et al. Preliminary report of a multi center Canadian phase III randomized trial of 3 months vs 8 months neoadjuvant androgen ablation prior to standard dose radiotherapy for clinically localized prostate cancer [abstract]. *Int J Radiat Oncol Biol Phys*. 2002;54:134.